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Abstract	Desmopressin is a synthetic analogue of the natural antidiuretic hormone arginine vasopressin. Over the years, it has been clinically used to manage nocturnal polyuria in children with enuresis. Various pharmaceutical formulations of desmopressin have been commercialized for this indication—nasal spray, nasal drops, oral tablet and oral lyophilizate. Despite the fact that desmopressin is a frequently prescribed drug in children, its use and posology is based on limited pediatric data. This review provides an overview of the current pediatric pharmacological data related to the different desmopressin formulations, including their pharmacokinetics, pharmacodynamics and adverse events. Regarding the pharmacokinetics, a profound food effect on the oral bioavailability was demonstrated as well as different plasma concentration–time profiles (double absorption peak) of the desmopressin lyophilizate between adults and children. Literature about maturational differences in distribution, metabolism and excretion of desmopressin is rather limited. Regarding the pharmacodynamics, formulation/dose/food effect and predictors of response were evaluated. The lyophilizate is the preferred formulation, but the claimed bioequivalence in adults (200 μg tablet and 120 μg lyophilizate), could not be readily extrapolated to children. Prescribing the standard flat-dose regimen to the entire pediatric population might be insufficient to attain response to desmopressin treatment, whereby dosing schemes based on age and weight were proposed. Moreover, response to desmopressin is variable, whereby complete-, partial- and non-responders are reported. Different reasons were enumerated that might explain the difference in response rate to desmopressin observed: different pathophysiological mechanisms, bladder capacity and other predictive factors (i.e. breast feeding, familial history, compliance, sex, etc.). Also, the relapse rate of desmopressin treatment was high, rendering it necessary to use a pragmatic approach for the treatment of enuresis, whereby careful consideration of the position of desmopressin within this treatment is required. Regarding the safety of the different desmopressin formulations, the use of desmopressin was generally considered safe, but additional measures should be taken to prevent severe hyponatremia. To conclude the review, to date, major knowledge gaps in pediatric pharmacological aspects of the different desmopressin formulations still remain. Additional information should be collected about the clinical relevance of the double absorption peak, the food effect, the bioequivalence/therapeutic equivalence, the pediatric adapted dosing regimens, the study endpoints and the difference between performing studies at daytime or at nighttime. To fill in these gaps, additional well designed pharmacokinetic and pharmacodynamic studies in children should be performed.
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REVIEW ARTICLE

Pediatric Pharmacology of Desmopressin in Children with Enuresis: A Comprehensive Review

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Abstract

Desmopressin is a synthetic analogue of the natural antidiuretic hormone arginine vasopressin. Over the years, it has been clinically used to manage nocturnal polyuria in children with enuresis. Various pharmaceutical formulations of desmopressin have been commercialized for this indication—nasal spray, nasal drops, oral tablet and oral lyophilizate. Despite the fact that desmopressin is a frequently prescribed drug in children, its use and posology is based on limited pediatric data. This review provides an overview of the current pediatric pharmacological data related to the different desmopressin formulations, including their pharmacokinetics, pharmacodynamics and adverse events. Regarding the pharmacokinetics, a profound food effect on the oral bioavailability was demonstrated as well as different plasma concentration–time profiles (double absorption peak) of the desmopressin lyophilizate between adults and children. Literature about maturational differences in distribution, metabolism and excretion of desmopressin is rather limited. Regarding the pharmacodynamics, formulation/dose/food effect and predictors of response were evaluated. The lyophilizate is the preferred formulation, but the claimed bioequivalence in adults (200 µg tablet and 120 µg lyophilizate), could not be readily extrapolated to children. Prescribing the standard flat-dose regimen to the entire pediatric population might be insufficient to attain response to desmopressin treatment, whereby dosing schemes based on age and weight were proposed. Moreover, response to desmopressin is variable, whereby complete-, partial- and non-responders are reported. Different reasons were enumerated that might explain the difference in response rate to desmopressin observed: different pathophysiological mechanisms, bladder capacity and other predictive factors (i.e. breast feeding, familial history, compliance, sex, etc.). Also, the relapse rate of desmopressin treatment was high, rendering it necessary to use a pragmatic approach for the treatment of enuresis, whereby careful consideration of the position of desmopressin within this treatment is required. Regarding the safety of the different desmopressin formulations, the use of desmopressin was generally considered safe, but additional measures should be taken to prevent severe hyponatremia. To conclude the review, to date, major knowledge gaps in pediatric pharmacological aspects of the different desmopressin formulations still remain. Additional information should be collected about the clinical relevance of the double absorption peak, the food effect, the bioequivalence/therapeutic equivalence, the pediatric adapted dosing regimens, the study endpoints and the difference between performing studies at daytime or at nighttime. To fill in these gaps, additional well designed pharmacokinetic and pharmacodynamic studies in children should be performed.

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Key Points

The current review summarizes the available literature concerning the pharmacology of desmopressin in children with enuresis.

Despite the fact that desmopressin has been available for more than 40 years, there remains a need for additional pharmacokinetic and pharmacodynamic studies in children.

To date, multiple research questions remain unanswered in the pediatric population: is there a double absorption peak? Is there a food effect? Is there bioequivalence/therapeutic equivalence? What is the optimal dosing regimen?

1 Introduction

The synthetic vasopressin analogue desmopressin has been used clinically for > 40 years in the treatment of enuresis (high, diluted urine output overnight) and central diabetes insipidus (CDI) [1–4]. In very high doses, desmopressin is also used to treat the congenital bleeding disorders, hemophilia A and von Willebrand disease, since it increases the von Willebrand factor, coagulation factor VIII and tissue plasminogen activator [5, 6]. Moreover, desmopressin has proven suitable to diagnose renal concentrating capacity (i.e. patients with CDI, urinary tract infections and suspected kidney damage) [7, 8]. The current review focusses on the use of desmopressin in children with enuresis, and does not discuss the use in diagnostic testing, nor in the treatment of children with CDI or congenital bleeding disorders.

Over the years, various pharmaceutical formulations of the antidiuretic desmopressin have been commercialized: nasal spray (since 1972), nasal drops (since 1972), oral tablet (since 1987) and oral lyophilizate (since 2005) [9]. All formulations have proven efficacy for children with enuresis, that is, resulted in a reduction of the number of wet nights. The conventional route of administration of desmopressin in adults and children used to be intranasal (IN) (drops or spray), since this route bypasses the gastrointestinal tract, leading to an increase in absolute bioavailability and hence a lower dose. However, in 2007, the Food and Drug Administration (FDA) announced a post-marketing drug safety warning about the use of nasal sprays in children, which was based on a limited number of case reports demonstrating that IN administration of desmopressin could potentially lead to severe hyponatremia and seizures [10]. These adverse events could be attributed to the variability in absorption and unintentional overdosing when using the nasal spray [11, 12]. Consequently, the use of IN formulations is no longer approved for treating enuresis in children in the United States of America (US) and most of the European countries. The latter required a definitive switch to oral formulations, despite the limited efficacy and safety data for these formulations in the pediatric population (i.e. lack of pharmacokinetic (PK) data of oral desmopressin, lack of bioequivalence studies, lack of availability of size-dependent dosing strategies, lack of safety studies). Over the years, additional research was performed to fill in some knowledge gaps [13–17, Dossche et al., submitted], but additional research is still required. Therefore, the aim of the current review is to provide an overview of the pediatric pharmacological data of the different desmopressin formulations, including their therapeutic use, PK, pharmacodynamics (PD) and safety. This overview contributes to the identification of which information is already available and which information is still missing to enable adapted desmopressin treatment strategies for children.

2 Structure and Physicochemical Properties

Desmopressin (1-desamino-8-D-arginine vasopressin, dDAVP), is a synthetic analogue of the natural antidiuretic hormone arginine vasopressin (AVP). Desmopressin was first synthetized in 1967 by deamination of the cysteine residue (prolonged activity due to a lipophilic N-terminal) and replacing the L-arginine configuration with the D-arginine configuration (reduced vasopressor activity due to changes in polarization of the molecule) (Fig. 1) [18]. The molecular formula of the nonapeptide desmopressin is $C_{46}H_{64}N_{14}O_{12}S_2$, with a molecular mass of 1069.224 g/mol. The active ingredient of the different formulations is desmopressin acetate. Desmopressin has a negative clog P (−7.711), which demonstrates the extreme hydrophilicity of this drug [19]. Desmopressin is a base with a pKa of 11.8 (strongest base).

3 Mode of Action

Desmopressin is mainly designed to treat nocturnal polyuria with increased free water diuresis by acting on the V_2 vasopressin receptors of the collecting ducts [20–22]. The drug binds to the V_2 receptor in the basolateral membrane of the collecting duct, stimulating the G_s-coupled protein to activate adenylate cyclase, leading to the formation of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). cAMP binds to protein kinase A, activating the phosphorylation cascade,

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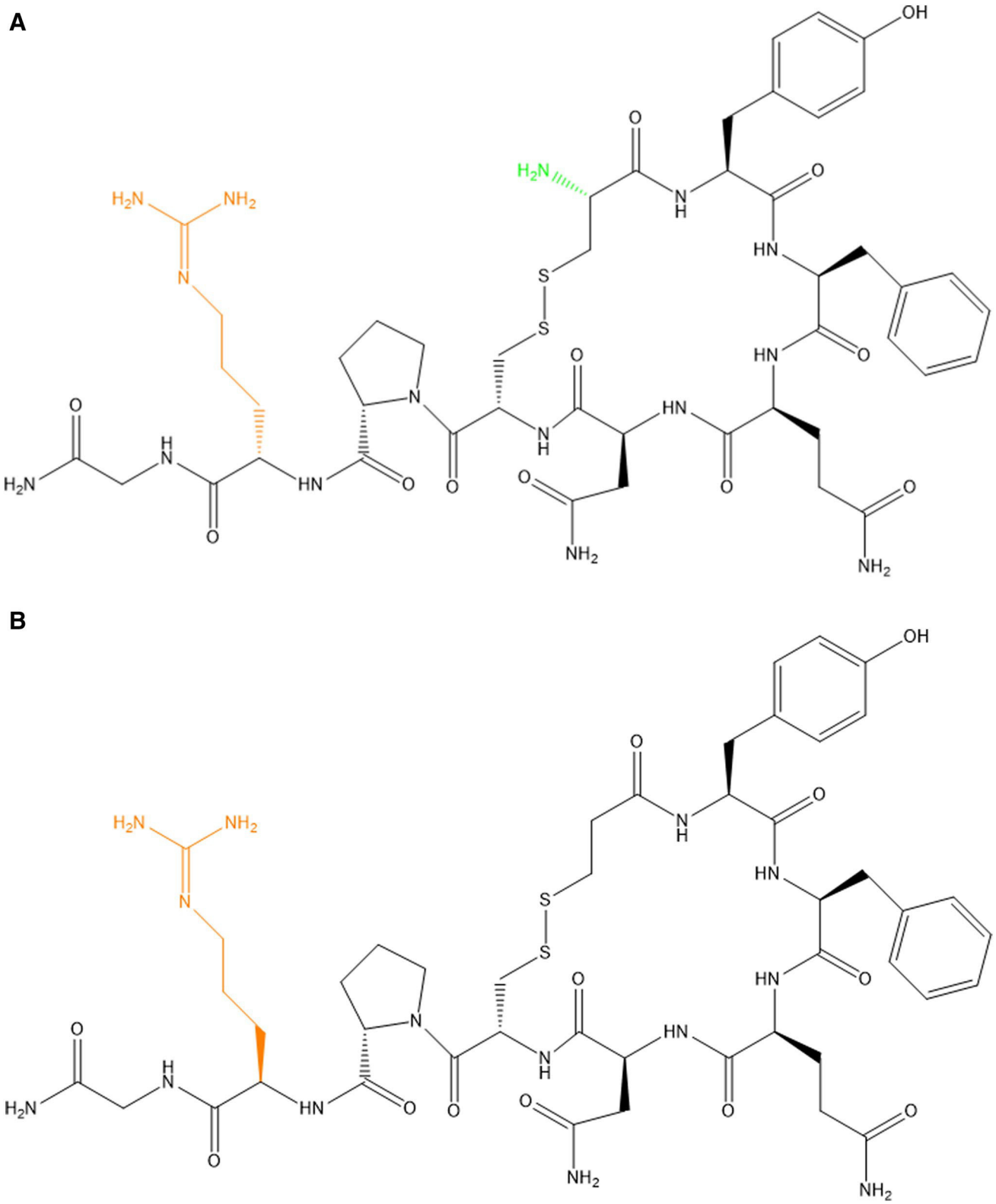

Fig. 1 Chemical structure of vasopressin (left, **a**) and desmopressin (right, **b**). Deamination (green) and L-arginine versus D-arginine configuration (*orange*) (made in Chemdraw 16®, PerkinElmer, USA)

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whereby the exocytosis of aquaporin-2 water channels from cytoplasmic aquaporin-2 water channel-containing vesicles towards the apical membrane of the collecting ducts is stimulated. Osmotic pressure (osmotic gradient established by NaCl and urea) between the lumen and the interstitium facilitates the water reabsorption through the water channels, resulting in urine concentration (Fig. 2) [23]. This almost exclusive V_2 receptor targeting results in antidiuresis by increased urinary concentration, without having a vasoconstrictor effect on the blood vessels.

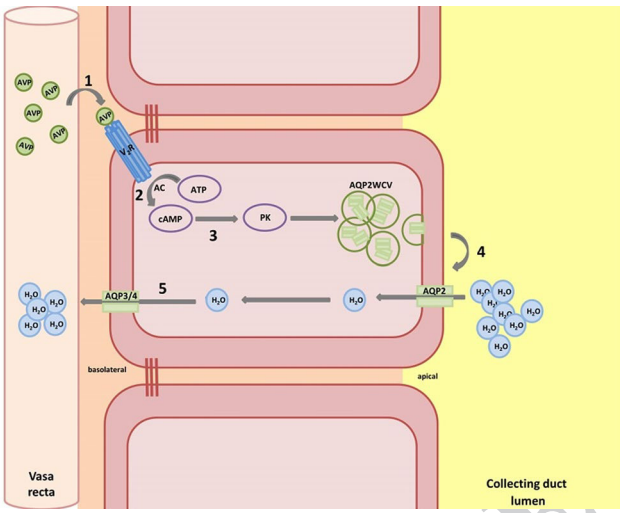

Fig. 2 Mechanism of action of desmopressin. 1: AVP binds to receptor, 2: receptor activates second messenger system, 3: cAMP binds PK, 4: exocytosis aquaporin channels, 5: water absorption. *AC* adenylate cyclase, *AQP2* aquaporin water channel *AQP2WCV* aquaporin 2 water channel-containing vesicles, *ATP* adenosine triphosphate, *AVP* arginine vasopressin, *cAMP* cyclic adenosine monophosphate, *PK* protein kinase A, V_2R V_2 vasopressin receptor (adapted from [24])

4 Therapeutic Use in Nocturnal Enuresis in Children

According to the International Children's Continence Society (ICCS), enuresis or bedwetting means micturition during sleep in a child of at least 5 years, the age at which bladder control should have been achieved [25]. Enuresis is subdivided into monosymptomatic (MNE) and non-monosymptomatic enuresis (NMNE), whereby for the latter, enuresis associated with symptoms of the lower urinary tract including daytime incontinence is observed [26]. The prevalence of enuresis is 12–25% in 5-year-old children, 6–8% in 8-year-old children, 2–3% in 12-year-old children and 0.5–1.7% in adulthood [27, 28]. The prevalence rate is higher in boys than in girls (2:1) [29], for which the reason is unclear up to now. The cure rate is defined as the achievement of complete dryness without arousal [30]. The annual spontaneous cure rate of enuresis is 14% in 5- to 9-year-old children, 16% in 10- to 14-year-old children and 16% in 15- to 19-year-old adolescents [30]. Not all patients with enuresis will cure spontaneously, and persisting enuresis is observed in 0.5–1.7% of the adolescents [11, 31]. Enuresis can potentially lead to distress, which has an impact on the child's self-esteem, social life, quality of sleep and school performance [32]. Both the impact on the well-being of the child as well as the persistence of enuresis in adolescents necessitates an effective therapy [33]. This therapy requires appropriate diagnosis of the enuresis type by proper screening of the patient, followed by administration and evaluation of the prescribed therapy [34]. Desmopressin and enuresis alarm are the only level 1 evidence and grade A first-line enuresis treatments recommended by the International Consultation on Incontinence [35].

Antidiuretic doses of the different formulations are listed in Table 1. For enuresis, it is recommended to administer oral desmopressin 1 h prior to bedtime, preferably without

Table 1 Antidiuretic doses of different desmopressin formulations (adapted from SPC Minirin® Ferring)

Formulation	Indication	Age	Dose	Dosing interval
Lyophilizate	Enuresis	Adult/child (> 5 years)	120–240 µg	1 per day, evening
	CDI	Adult/child (> 5 years)	60–120 µg	3 per day
	Nocturia	Adult/child (> 5 years)	60–240 µg	1 per day, evening
Nasal spray	CDI	Adult	10–20 µg	2 per day
Nasal drops	CDI	Adult	10–20 µg	2 per day
IV/IM/SC injection	CDI	Adult	1–4 µg	1 per day
	CDI	Child	0.4 µg	1 per day
PO tablet	Enuresis	Adult/child (> 5 years)	200–400 µg	1 per day, evening
	CDI	Adult/child (> 5 years)	100–200 µg	3 per day
	Nocturia	Adult/child (> 5 years)	100–400 µg	1 per day, evening

CDI central diabetes insipidus, *IM* intramuscular, *IV* intravenous, *PO* per oral, *SC* subcutaneous

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simultaneous food intake [15, 36, 37]. 2 weeks after starting desmopressin therapy, dosages should be individually adapted, preferably according to anti-enuretic and anti-diuretic effects. In enuresis, the therapy should be re-evaluated every 3 months (treatment withdrawn for at least 1 week) to monitor if further treatment is required [38]. A structured withdrawal is required when discontinuing desmopressin treatment, to evaluate if enuresis reoccurs. This structured withdrawal is preferred over sudden termination, since it results in an increasing success rate and a decreasing relapse rate [39, 40]. Moreover, dose-dependent withdrawal (lowering the dose) results in less wet incidents in comparison with time-dependent withdrawal (increasing time between doses) and is therefore the preferred approach [41, 42].

4.1 Desmopressin and Alarm Therapy

Several authors evaluated if combination therapy could be more beneficial than desmopressin monotherapy. Evaluating different types of therapy is necessary, however the results of these studies should be carefully interpreted since the lack of subtyping of enuresis might result in confounded results. Ideally, to assess these therapies, only carefully compared patients can be used as their own controls. Moreover, definitions about response rate of different therapies should be carefully interpreted, since for desmopressin therapy the decrease of number of dry nights is often used, whereas for alarm therapy the percentage of nights the child arouses for urination is determined [30]. Perrin et al. [43] and Peng et al. [44] performed a systematic literature review on alarm versus desmopressin monotherapy in children with MNE, showing that alarm therapy was preferred due to the lower relapse rate. However, the latter is only applicable to motivated children, since a much higher dropout rate was noted with the alarm [45, 46]. The latter conclusions were confirmed by a network meta-analysis performed by Song et al. [47].

4.2 Desmopressin and Other Drugs

Lee et al. [48] evaluated the efficacy of desmopressin monotherapy versus desmopressin combined with oxybutynin (anticholinergic) and versus imipramine (tricyclic antidepressant) monotherapy in children with enuresis (5–15 years). The authors concluded that the efficacy of combination therapy was higher in comparison with both monotherapies. The latter was inconsistent with the results found by Naitoh et al. [49], where no significant differences between alarm monotherapy, desmopressin or imipramine and alarm combination therapy were observed. In a pilot study, De Guchtenaere et al. [50] demonstrated that addition of early morning furosemide (diuretic) significantly lowered nocturnal diuresis rates in children with MNE resistant to desmopressin. Alloussi et al. [51] evaluated the combination of propiverine (antimuscarinic) and desmopressin in children with bedwetting. This combination therapy was highly effective, but a further decrease of the relapse rate (21.5%) and fine tuning of dosing regimens was still required. This combination was then optimized by Jabbour et al. [52], whereby the relapse rate decreased to 13%. However, it should be noted that the reported relapse rates might be an overestimation of the real-life situation, since only children who were unresponsive to monotherapy were included. Park et al. [53] demonstrated that a combination of desmopressin and an anticholinergic drug (oxybutynin, tolterodine [antimuscarinic], propiverine [antimuscarinic]) resulted in a more effective and faster response than desmopressin monotherapy. A possible role for the combination of desmopressin and oxybutynin in desmopressin monotherapy non-responders was confirmed by Radvanska et al. [54]. Azarfar et al. [55] demonstrated that the combination of desmopressin and tolterodine had a lower relapse rate than desmopressin and oxybutynin combination therapy. Kamperis et al. [56] administered either a combination of indomethacin (non-steroidal anti-inflammatory drug) and desmopressin, or a placebo and desmopressin, to children with MNE and desmopressin-resistant nocturnal polyuria. The authors concluded that there was an added effect of indomethacin to desmopressin therapy, leading to a greater reduction in nocturnal urinary output. However, the number of wet nights was not significantly different between combination and monotherapy.

5 Pharmacokinetics

The nasal route of administration is traditionally preferred for peptide drug delivery, since the relatively large surface area, thin epithelium and rich vascularization facilitate the absorption of these peptides. However, higher inter- and intra-subject variability in PK was observed following IN administration [57]. Subsequently, alternative routes of administration, such as the oral lyophilizate, were explored. Table 2 gives an overview of the PK parameter values of desmopressin administered via different formulations in humans. Only five papers described PK studies performed in the pediatric subpopulation for treatment of enuresis (highlighted in Table 2) [13–14, 15–17, 58, Dossche et al., submitted].

5.1 Absorption

Oral desmopressin is absorbed relative rapidly via a paracellular route in the duodenum and the proximal jejunum, reaching maximal plasma concentrations (C_{max}) between 0.6 and 1.5 h after administration (T_{max}) in healthy male

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Table 2 Pharmacokinetic parameters of desmopressin in humans after various routes of administration

Route of administration	Disease state	Age (years)	Dose (μg)	CL (L/h)	V_d (L)	$T_{½el}$ (h)	AUC_{inf} (pg h/mL)	C_{max} (pg/mL)	T_{max} (h)	*F* (%)	References
PO tablet	Healthy	20–57	200				25.4	13.6	1.2	0.1	[61]
	Diabetes	30–43	200			2.0	50.3	16.2	1.5		[76]
	Diabetes	30–43	200			2.0	50.3	16.2	1.5		[76]
	Diabetes	30–43	200			2.0	50.3	16.2	1.5		[76]
	Healthy	55–75	200				23	6.2	1.5	0.08	[66]
	Healthy	23–45	400			2.5	90.4	25.4	1.3		[64]
	Nocturia	65–78	400			3.3	70.7	14.2	1.5		[77]
	Healthy	18–49	400				85.5	23.2	1.2		[78]
	Healthy	18–49	400				91.2	28.2	1.1		[78]
	Healthy	20–35	400			2.3	70.8	22.0	1.0		[36]
	Healthy	20–35	50			1.4	1.7[c]		1.0		[79]
	Healthy	20–35	100			1.9	3.2[c]		1.0		[79]
	Healthy	20–35	200			2.4	7.0[c]		2.0		[79]
	Diabetes	21–52	200						1.0		[79]
	Healthy	19–45	600			2.3	132.0	32.0	1.2		[80]
	Healthy	18–45	600			2.7	229.6	64.2	1.0		[63] (fasted)
	Healthy	18–45	600			2.5	88.7	20.19	2.0		[63] (fed)
PO spray	Healthy	21–29	160				59.0	15.5	1.0		[81]
	Healthy	21–29	240				110.9	29.8	0.7		[81]
	Healthy	21–29	320				137.3	41.6	0.9		[81]
IN powder spray	Healthy	20–32	19			2.8	372.0	103.3	0.8		[82]
IN liquid spray	Healthy	20–57	20				63.0	21.3	1.0	3.4	[61]
	Healthy	20–32	9.5			2.7	135.4	34.1	0.8		[82]
	Healthy	20–34	20				116.9	31.2	0.7		[57]
	Healthy	20–34	20				108.9	30.0	0.6		[57]
	Diabetes	**11–16**	**10–25**								[79]
	Diabetes	30–43	20			2.2	79.9	25.8	0.7		[76]
SC injection	Healthy	20–57	2				202.5	62.3	0.7		[61]
IV injection	Healthy	20–57	2			1.3	122.3			100	[61]
	Enuresis	**7–16**	**2**			**1.5**		**164**	**0.5–1**	**100**	[58]
	Healthy	22–46	2	10.4	28.2	2.0	197			100	[65]
	Healthy	55–75	2	6.6	11.3	3.1	302	181		100	[66]
	Renal dysfunction	20–76	0.3 μg/kg	1.6	22[d]	9.7				100	[83]
PO lyophilizate	Healthy	20–32	240			2.1	67.4	17.9	1.5	0.25	[82]
	Enuresis	**7–16**	**120**	**4982**[a]	**23,346**[b]						[15] [e]
	Enuresis	**6–13**	**240**	**2330**[a]	**8510**[b]						[13]

Table 2 (continued)

Route of administration	Disease state	Age (years)	Dose (μg)	CL (L/h)	V_d (L)	$T_{½el}$ (h)	AUC_{inf} (pg h/mL)	C_{max} (pg/mL)	T_{max} (h)	*F* (%)	References
	Enuresis	**0.5–8**	**60–240**	**1826**[a]	**4018**[b]	**1.6**	**104**	**41**	**1**		**Dossche et al., submitted** [17] [f]
	Enuresis	**0.5–16**	**0–480**	**4960**[a]	**1090**[b]						

Bolded text indicates pharmacokinetic parameters of desmopressin in children

AUC_{inf} area under the plasma concentration–time curve, *CL* clearance, *C_{max}* maximal plasma concentration, *F* absolute bioavailability, *IN* intranasal, *IV* intravenous, *PO* per os, *SC* subcutaneous, *SL* sublingual, *$T_{½el}$* elimination half-life, *T_{max}* time at maximal plasma concentration, *V_d* volume of distribution

[a] CL/F

[b] V_d/F

[c] pmol/h

[d] V_{ss}

[e] Population PK estimated based on Osterberg et al. [13] and De Bruyne et al., [14]

[f] Population PK estimated based on Osterberg et al. [13], De Bruyne et al. [14] and Dossche et al.

adults [59, 60]. Overall, the oral bioavailability in healthy adults is extremely low (0.08–0.16%), since desmopressin is enzymatically degraded in the lumen of the gastrointestinal tract and the high molecular weight of desmopressin makes the paracellular absorption inefficient [19]. Moreover, absorption via a transcellular route seems less likely, due to the negative clog P (−7.711) observed for desmopressin. Osterberg et al. [13] stated that the oral absorption process of desmopressin might be different for children (enuresis, ages 6–13 years), since the mean transit time was significantly different in comparison with adults (children: 0.21 h, adults: 0.48 h). This observation could be attributed to a maturational change in absorptive surfaces, gastric emptying and/or intestinal motility. The bioavailability following IN administration in healthy adults is better (3–5%) when compared with oral (PO) administration [61].

Gasthuys et al. [16] evaluated the PK of desmopressin lyophilizate in growing piglets (Belgian Landrace × large white; 8 days, 4 weeks, 7 weeks, 6 months of age) using population PK modeling. This was the first study demonstrating a dual sequential absorption process, with a double peak present in the absorption phase, probably attributed to transmucosal absorption in the oral cavity and the small intestine. This observation was also hypothesized by Michelet et al. [62], who found a discrepancy when linking their previously published PK model [15] to their PD parameters in children. The authors observed a significant effect of the formulation on the IC_{50} (half maximal inhibitory concentration), which is physiologically implausible since only at the PK side a formulation effect is expected. A possible explanation was that the model was not able to capture the absorption part due to the sparse sampling design applied in the human pediatric studies, resulting in a mismatch between the PK and the PD models. Two possible hypotheses were proposed to explain this mismatch: (1) fast absorption of the lyophilizate, potentially missing a larger absorption peak or (2) occurrence of two absorption peaks. To confirm one of these hypotheses, Dossche et al. performed a clinical PK/PD study in children applying a rich sampling design during the absorption phase. In this study, the double absorption peak was confirmed in growing children (6 months to 8 years of age, especially 60 and 120 μg lyophilizate). Moreover, Michelet et al. [17] reanalyzed their previously published pediatric PK/PD model including the newly generated clinical data, which resolved the previous stated discrepancy and confirmed the double absorption peak hypothesis.

Rittig et al. [36] investigated the effect of food intake on the absorption after PO administration of 400 μg desmopressin to healthy adults aged 20–35 years. Concomitant administration of desmopressin and a standard meal (2199 kJ, Big Mac®) and administration of desmopressin 1.5 h after eating a standard meal resulted in a reduced (50% lower C_{max}) and delayed absorption (longer T_{lag} and higher T_{max} with

an increase from 0.25 h to 0.5 h and 1 h to 1.5 h, respectively) in comparison with fasted patients. These observations were confirmed in a more recent study performed in Chinese healthy adults aged 18–45 years [63]. Two possible explanations were proposed for these observations: (1) the binding of desmopressin to food particles or (2) the interaction of food with intestinal metabolic activity (increase in peptidase production). Michelet et al. [15] pooled pediatric data from two PK desmopressin trials in children and developed a model using a population PK approach on a sparse sampling set to understand the effect of food intake on the absorption of desmopressin (120 µg lyophilizate and 200 µg tablet). The effect of concomitant food intake was found to be clinically significant and might influence the bioavailability and therefore the optimal dosing of desmopressin [17]. The latter was confirmed in another analysis, with the addition of lyophilizate data generated in the recently performed study of Dossche et al. in fasted younger children.

Callréus et al. [64] investigated the effect of the gastrointestinal motility and gastrointestinal secretion by administering erythromycin (increasing motility, 250 mg every 6 h, first dose 3 days before the study and last dose at − 1 h) and loperamide (slowing motility, 4 mg, − 24 h, − 12 h and − 1 h) prior to PO administration of 400 µg desmopressin to healthy volunteers (23–45 years). A significant increase in C_{max} and T_{max} was observed when desmopressin was administered after pre-treatment with loperamide, while no significant difference in absorption was observed with erythromycin. The latter observations still need to be confirmed in the pediatric population.

5.2 Distribution

The volume of distribution (V_d) of desmopressin after IV injection is 28.2 L in 22- to 46-year-old subjects and 11.2 L in 55- to 75-year-old subjects [65, 66]. In children aged 6–12 years, the mean population PK estimate of apparent V_d after administration of an oral lyophilizate was 8510 L, which would correspond to a systemic V_d of 21.3 L (assuming 0.25% bioavailability) [13]. This result was in accordance with the result (8237 L) obtained by Michelet et al. [15]. The latter authors also observed an effect of body weight on V_d, indicating that dose adjustment might be required. Information about the plasma protein binding of desmopressin is rather scarce. Lawton and Witty [19] mentioned that 50% of the absorbed desmopressin binds to plasma proteins. Desmopressin does not cross the blood–brain barrier after IV administration to patients aged 36–72 years [67]. Burrow et al. [68] determined desmopressin concentrations in breast milk in a 23-year-old woman with diabetes insipidus. They concluded that desmopressin seems to be a safe therapy, since only traces of desmopressin (max. 7 ng/L at 40 min post-administration) were found in breast milk. However, it should be noted that this study was only performed in one patient, so additional studies are required.

5.3 Metabolism

An in vitro study in rats demonstrated that 20% of desmopressin was inactivated by the liver and only a small fraction by the kidney [69]. Fjellstad-Paulsen and Lundin [70] determined the degradation of AVP and desmopressin in human renal microvilli brush-border membranes and human liver membranes. Arginine vasopressin was found to be degraded in the kidney at both the C- and N-terminus as well as by disulphide cleavage when the cofactor glutathione was present, and was found to be stable without this cofactor. However, degradation of desmopressin in the kidney was negligible even when glutathione was present. No degradation was observed when desmopressin was incubated with purified liver cell membranes, since desmopressin might undergo receptor-mediated endocytosis followed by intracellular metabolism. This theory was also supported by Lundin et al. [71], where rapid removal of desmopressin from the incubation medium was observed after incubation of desmopressin with liver tissue slices. Removal can be a consequence of binding to hepatic vasopressin receptors or internalization followed by intracellular degradation. Enzyme-dependent proteolysis of desmopressin by pancreatic enzymes in jejunal and ileal juice also occur. Degradation of desmopressin appears slower in jejunal than ileal juice; since it is pH dependent, it is more stable at acidic pH [72]. To confirm the theory of enzyme-dependent proteolysis of desmopressin, concomitant administration of aprotinin (broad-spectrum proteinase inhibitor) and desmopressin was studied. A concentration-dependent inhibition of desmopressin degradation was indeed observed, enhancing the bioavailability of orally administered desmopressin [73].

5.4 Excretion

The mean population PK values of apparent clearance for children (6–12 years) and adults (18–54 years) was 2330 L/h and 2930 L/h, respectively [13, 15]. The main route of elimination of desmopressin is renal excretion. Fjellstad-Paulsen et al. [61] determined the urinary excretion after IN, subcutaneous (SC) and PO administration (IN: 20 µg; SC: 2 µg; PO: 200 µg) in healthy adults aged 20–57 years. Forty-eight percent, 92% and 65% of the amount absorbed after SC, IN and PO administration, respectively, was excreted in urine within 24 h. However, the renal fraction in the pediatric population still needs to be determined. The renal fraction of desmopressin after IV administration (4 µg) was 39% [74]. Moreover, Agerso et al. [74] investigated the correlation between creatinine clearance and renal clearance in both healthy volunteers and renally impaired patients (aged

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49–68 years) and found that both renal and non-renal excretion of intravenous desmopressin varied with creatinine clearance. A decrease of 1.67% in creatinine clearance led to a 1.74% decrease in renal clearance and a 0.93% decrease in nonrenal clearance of desmopressin. This observation could possibly be attributed to the association of renal impairment and a decrease in hepatic metabolism. Moreover, a prolongation of the elimination half-life ($T_{½el}$) was observed. Since desmopressin is only partially eliminated (39%) by the kidney, the total clearance of desmopressin is less affected by renal function. Consequently, desmopressin is still well tolerated in renally impaired patients. However, when administering high doses of desmopressin, adverse effects may occur in those patients, so great caution should be exercised when establishing the exact dosing regimen. Lundin et al. [71] determined the excretion of desmopressin in bile after various routes of administration (intraduodenal, intrajugular and intraportal) in one conscious pig (Swedish Landrace, 4 months old). Only low concentrations of desmopressin were retrieved in bile, < 1% of the available dose. The $T_{½el}$ after PO administration of desmopressin is prolonged in comparison with endogenous AVP, since its enzymatic degradation in liver and kidney are slower [75].

6 Pharmacodynamics

About 6–10% of children aged 7–8 years suffer from bedwetting; however, only 60–70% are responders (complete or partial responders) to desmopressin treatment [84–86]. Despite the low oral bioavailability, the plasma concentrations are sufficient to achieve antidiuretic effects. This can be attributed to high receptor affinity and binding capacity of desmopressin to the V2 receptor [19]. Ideally, the duration of action of desmopressin for treating bedwetting should vary between 8 and 11 h, since longer durations could induce adverse effects (hyponatremia, seizures and abdominal pain). Multiple studies demonstrated the efficacy (reducing the number of wet incidents, reducing 24-h urine production) of the different desmopressin formulations in children with enuresis [87–93].

6.1 Formulation Effect

Various formulations of desmopressin have been used to treat bedwetting. De Guchtenaere et al. [94] compared an oral lyophilizate tablet (120 µg) with a conventional tablet (200 µg) in children aged 12.1 ± 2.5 years (enuresis) and concluded that the lyophilizate has a higher concentrating capacity and requires a shorter time to reach maximal effect in comparison with the tablet. De Bruyne et al. [14] performed a relative bioavailability study of a 200-µg tablet compared with a 120-µg lyophilizate in children aged 5–18 years (enuresis). Relative bioavailability between both formulations was found, but the smaller inter- and intra-subject variability in plasma concentration and better predictability of plasma concentrations makes the lyophilizate more reliable in comparison with the tablet. However, Michelet et al. [15] constructed a population PK model based on pooled data from the studies of Osterberg et al. [13] and De Bruyne et al. [14], whereby the claimed bioequivalence between the two formulations in adults (200-µg tablet and 120-µg lyophilizate) could not be extrapolated to children. Moreover, in a follow-up modeling study, after inclusion of the data generated by Dossche et al., Michelet et al. [17] found that bioequivalence of the two formulations could not be claimed in children due to differences in absorption and the impact of food and age (0.5–16 years). Lottman et al. [95] also compared efficacy and safety between the lyophilizate (120–240 µg) and the tablet (200–400 µg) in children (5–15 years) with enuresis. Both formulations were well tolerated and no adverse effects related to the study treatment were observed. The incidence of enuresis events measured during a 6-week cross-over study (3 weeks formulation one [tablet or lyophilizate] followed by 3 weeks formulation two [lyophilizate or tablet]) was comparable between both formulations. Higher compliance was achieved with the lyophilizate, since it circumvents the difficulties observed when children need to swallow desmopressin tablets. The latter was also confirmed by Juul et al. [96], whereby a higher patient compliance and consequently increased treatment outcome was observed with the lyophilizate (5–15 years, enuresis). Rembratt et al. [66] determined the PD parameters of desmopressin (PO: 200 µg; IV: 2 µg) and the influence of the circadian rhythm on those parameters in male patients aged 55–75 years (high incidence of nocturia). The PD effects were almost identical for both formulations during the first 6 h; however, the duration of action of the IV administration lasted longer. When the PD parameters of desmopressin administration during daytime or nighttime are compared, the effects on urine production and osmolality were prolonged to 12 h at nighttime, possibly due to the additive effect of desmopressin and endogenous vasopressin at night. This observation should also be evaluated in the pediatric population.

6.2 Dose–Effect

Schulman et al. [22] performed an 8-week dose titration study with a desmopressin tablet in children with bedwetting (aged 6–16 years). The starting dose was set at 200 µg, followed by an increase in 200-µg increments (evaluation every 2 weeks) until dryness or the maximum dose of 600 µg was achieved. A linear dose–response relationship was noted, meaning that the reduction in the number of wet nights per 2 weeks (number of nights reduced by 50% compared with

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the baseline) is linearly related to the administered desmopressin dose.

Vande Walle et al. [37] performed one of the first dose-titration studies (30, 60, 120, 240, 360 and 480 µg) of desmopressin lyophilizate to assess the PD measurements in enuretic children aged 6–12 years (urinary volume, osmolality and duration of action). A decline in urinary output and maximum osmolality (> 800 mOsm/kg bodyweight) was observed 1 h post-administration for the 60- to 480-µg dosing. Maximum effect of the 30-µg dose was also achieved after 1 h, but maximum osmolality was lower in comparison with the other doses. Since the maximum effect is reached 1 h after dosing, it is important to administer the lyophilizate 1 h prior to bedtime. The duration of action is around 6 h for 120 µg and > 8 h for > 120-µg doses, enabling control of diuresis for 7–11 h (≈ approximately one night). Since the maximum osmolality, duration of action and urinary output are comparable between the 240-, 360- and 480-µg doses and most enuresis events occur during the first 2 h of sleep [97], a dose range of 120–240 µg should be sufficient. The lower doses also reduce the risk of adverse effects. Ferrara et al. [98] performed a 9-week dose titration study with a desmopressin lyophilizate in children with enuresis (aged 5–18 years), followed by an observation period of 3 months (responders). The starting dose was set at 120 µg, followed by an increase to 180 µg (partial responders at 120 µg, evaluation after 3 weeks) and 240 µg (partial responders at 180 µg, evaluation after 3 weeks). The non-responders were excluded from the study. In this study, only a limited number of patients had a further improvement of symptoms (14.3%) or were complete responders (9.5%) after titrating the dose to 180 µg. No improvement of the symptoms was observed when the dose was further titrated to 240 µg, which demonstrates the need to prescribe the right dose to the right patient. Michelet et al. [17] evaluated if the current standard dosing regimens (120 µg) were sufficient for children who were not fasted when taking desmopressin before bedtime. The authors concluded that the current dosing using lyophilizate was inappropriate, whereby new and simple simulated dosing schemes based on age or weight were proposed (age based: 30 µg [< 2 years], 60 µg [2–4 years], 120 µg [4–8 years], 180 µg [8–12 years], 240 µg [+ 12 years]; weight based: 45 µg [< 12.5 kg], 90 µg [12.5–25 kg], 180 µg [25–50 kg], 360 µg [50–100 kg]).

6.3 Food Effect

Rittig et al. [36] investigated the effect of food intake on the antidiuretic action of desmopressin after PO administration of two 200-µg tablets to healthy adults aged 20–35 years. Despite the reduced and delayed absorption of desmopressin, concomitant administration of a standard meal and desmopressin did not significantly alter the antidiuretic response to desmopressin 400 µg during the first 4 h post-administration. However, the duration of action was prolonged in fasted pediatric patients in comparison with fed pediatric patients, since the plasma drug concentrations were significantly higher [17].

6.4 Predictors of Response

An anti-enuretic response, namely a reduction in number of wet nights of 100% (complete responder) or of 50–99% (partial responder), is achieved in 60–70% of the children treated with desmopressin [25, 35, 99]. Thirty to forty percent of the patients are non-responders, probably attributed to small nocturnal bladder capacity and detrusor-dependent nocturnal enuresis. Despite the proven success rate, a high relapse rate (78%) after short-term desmopressin treatment is observed, whereas the relapse rate was decreased when administration was maintained for longer [35]. The high relapse rate and the number of non-responders render it necessary to use a pragmatic approach for the treatment of bedwetting, whereby careful consideration of the position of desmopressin within this treatment is required.

Different underlying pathophysiological mechanisms of enuresis could explain the differences in response to desmopressin [100]. An anti-enuretic response of desmopressin is expected when patients are able to increase their urinary osmolality [11]. Nevéus et al. [58] studied the difference in PD effects after IV injection of desmopressin (2 mg) to children aged 7.6 and 16.2 years (enuresis). Half of the study population ($n = 6$) were responders and half ($n = 6$) were non-responders to the treatment. Enuresis only occurred in the non-responder group. It appears that in both responders and non-responders a low nocturnal urine production and high morning urine osmolality was present. A higher urinary output of less concentrated urine was produced by the responders, whereas non-responders voided with smaller bladder volumes. The latter is probably due to instability of the bladder. Rushton et al. [101] evaluated if maximum functional bladder capacity (as a percent of predicted bladder capacity) could predict response to desmopressin in enuretic children aged 8–14 years. The authors observed that when the maximum functional bladder capacity exceeded the mean capacity of the studied patients (= 70% of the age predicted capacity), the likelihood of response increased twofold. Hogg and Husmann [102] found that there was a good correlation (91%) between successful therapy response to desmopressin and a positive familial nocturnal enuresis history, whereas a poor correlation was noted when the family history was negative (7%). The latter was in contrast to the results found by Schaumburg et al. [103], where successful therapeutic response could not be predicted by a positive family history. Devitt et al. [104] investigated the relationship between nocturnal concentrations of AVP and the

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response to desmopressin, which combined with physiological factors might predict a successful response. The authors observed a correlation between response to desmopressin and nocturnal AVP concentrations, which is influenced by neuronal patterning during early infancy (maturation of neuronal networks involving the hypothalamic pituitary axis and AVP production). The best predictive physiological factors were (1) breast feeding; (2) mean nocturnal AVP concentration and (iii) height. Moreover, an inverse correlation with low birth weight and poor linear growth was noted. Kruse et al. [105] evaluated predictive factors (age, gender, heredity, sleep pattern, previous treatments, number of wet incidents and dosing regimens) for successful desmopressin treatment (6–12 years, MNE). No specific predictors could be identified, possibly because the pathology of enuresis needs to be considered to evaluate the predictors and the success rate of the therapy. Van Herzeele et al. [106] also evaluated predictive parameters for desmopressin response (number of wet nights a week, fluid intake, daytime voiding frequency, diuresis, age, body mass index, country, family history and sex), whereby only nocturnal diuresis volume (volume of 180, 300, 400 mL: 11%, 20%, 60% complete responders, respectively) and the number of wet nights a week (limited number increases response rate) were considered good predictors (aged 5–15 years, enuresis). When looking at the demographic variables, only age was considered significant; the response rate in younger children was significantly lower than in adolescents. Van Herzeele et al. [107] also evaluated if the patient's motivation and compliance can influence the response rate. The compliance in 723 children treated with desmopressin tablets for 6 months or less was determined and the authors concluded that a decreased compliance was related to a lower response rate.

The PD response of desmopressin is different between male and female patients, with a higher antidiuretic efficacy observed in adult females [12, 65]. Juul et al. [108] examined the sex difference in antidiuretic response in patients with nocturia (> 2 voids/night and serum sodium concentration > 135 mmol/L) and healthy volunteers. The mean decrease in nocturnal urine volume was higher in females than males. Moreover, the decrease in sodium plasma concentrations was more profound in females, potentially causing hyponatremia in those patients, whereby a narrower therapeutic window should be applied. The exact mechanisms to explain those differences are still unidentified, but different expression of the V_2 receptor in males versus females could be a possible explanation. Liu et al. [109] examined the expression of V_2 receptor mRNA and protein in kidneys of female and male Sprague–Dawley rats, and linked the dimorphic traits between the sexes and phenotypic variability among female heterozygotes to the second 'silenced' X-chromosome. Some genes escape the inactivation of the second X-chromosome, whereby a variability in gene expression could be observed. Carrel and Willard [110] demonstrated that the V_2 receptor has a high probability to escape inactivation, potentially leading to expression of this gene from both X-chromosomes in females. However, further research is required to completely understand the sex differences in antidiuretic response of desmopressin. Schroeder et al. [111] determined if there were sex-related differences in renal sensitivity to desmopressin in Danish children with nocturnal enuresis (mean age 9.2 years). In this study, a greater percentage of girls than boys had a long-term effect of the lowest desmopressin lyophilizate dose, confirming the theory that girls could possibly be more sensitive to desmopressin than boys. However, the authors noted that the difference between girls and boys was rather small, necessitating additional studies to further confirm this theory. When administering the tablet and the nasal spray, no sex-related differences were observed, possibly attributed to the fact that sex differences were only observed at the lowest desmopressin doses, as the doses of the tablet and the nasal spray were high. For both boys and girls, no hospital diagnoses of hyponatremia were documented for any of the mentioned formulations.

7 Adverse Events

The safety of different desmopressin formulations has been thoroughly researched. The use of desmopressin is considered safe but additional preventive measures should be taken in order to prevent severe hyponatremia. In 1987, Fjellstad-Paulsen et al. [112] compared the tolerability of IN and PO desmopressin administration in children with enuresis (aged 6–14 years) and did not observe any significant adverse events related to these formulations (two patients experienced nasal discomfort and three patients experienced epistaxis). Li Volti et al. [113] and Akoğlu et al. [114] did not observe any effect on nasal cytology and mucociliary clearance after 6 months of nasal spray therapy in children aged 6–16 years. Desmopressin does not affect sleep directly, but responders exhibit more rapid-eye-movement sleep than non-responders, which might be caused by differences in vasopressin secretion [115]. Dehoorne et al. [116] evaluated clinical symptoms of water intoxication after administration of desmopressin nasal spray to 2043 pediatric patients (1999–2004). Fifteen children (aged 6–15 years) were identified to have water intoxication resulting in vomiting, headache, decreased consciousness, seizures and hyponatremia. The authors concluded that these symptoms were secondary to a prolonged desmopressin bioactivity, that is, prolonged maximal urinary concentration capacity and delayed restoration of daytime diluting. Moreover, Glazener and Evans [99] found 21 case reports of water intoxication (< 1,993), probably due to over-drinking at bedtime, as a maximum concomitant fluid intake during the night of

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200–240 mL was recommended. The latter is also confirmed by Thumfart et al. [117], Vande Walle et al. [9], Lucchini et al. [118] and Kamperis et al. [34]. Del Gado et al. [119] evaluated the safety of desmopressin using either the nasal spray or the tablet (initial dose: 20 µg; maximum dose: 40 µg). Only transient, mild side effects were observed. Kano and Arisaka [120] administered desmopressin nasal spray (10 µg, uptitrated to 20 µg when patients remained incontinent after 4 weeks) for long-term treatment (between 12 and 24 weeks) of children (aged 6–15 years) diagnosed with enuresis. The authors did not observe any significant adverse effects (one patient had acute rhinitis and one patient had an event of excitement) and concluded that the nasal spray is safe and effective for long-term treatment in children with enuresis. The latter was also concluded in the studies performed by Knudsen et al. (MNE [121]), Hjälmås et al. (MNE [88]) and Läckgren et al. (refractory enuresis [89]). Alloussi et al. [122] reviewed 99 studies (7422 patients, children aged > 5 years to adolescents), whereby a low number of case reports [123–125] and post-marketing safety data demonstrated a higher risk of hyponatremia when administering nasal formulations. Despite the fact that hyponatremia events are rather rare, the authors made a plea for safety analysis, and not only limited to nasal formulations, by using routine laboratory testing. In comparison with IN administration, PO administration has a decreased risk of hyponatremia. Robson et al. [10] determined potential risk factors for hyponatremia: (1) excessive fluid intake, (2) overdosing, (3) age (< 6 years) and (4) interactions with other drugs. Van Herzeele et al. [126] performed a prospective study to determine the safety of desmopressin tablets in 744 children with bedwetting (aged 5–15 years), whereby no drug-related adverse events were observed. Ferrara et al. [127] included 237 enuretic children (5–18 years) to determine the adverse events of the lyophilizate based on their personal experience. Twenty-two children reported mild transient adverse events. This study demonstrated that the lyophilizate is safe to treat children with enuresis. Juul et al. [108] demonstrated a sex difference in incidence of hyponatremia in adults, whereby adaptation of the dose stratified by sex was required. For adult women, a dose of 25-µg lyophilizate is considered efficacious and safe, whereas for adult men this dose was 50- to 100-µg lyophilizate. To date, the latter still needs to be determined in the pediatric population, since only non-gender adapted doses (60- to 360-µg lyophilizate) were proposed in this population.

8 Conclusion

For more than 40 years, desmopressin has been mostly prescribed to children (approximately 90%) and investigated in adults. Despite the fact that desmopressin is generally accepted for the treatment of children with enuresis, there are still a lot of research questions that need to be addressed concerning the pharmacology of desmopressin in the pediatric population. The current review summarized the available literature concerning this topic, whereby the need for additional PK/PD studies in children was demonstrated. The following research questions remain:

- *Double absorption peak* Due to the rich sampling strategy applied in a recent study (Dossche et al.), a double absorption peak was observed in the plasma concentration–time profiles of the younger children administered a lyophilizate (aged 6 months to 8 years). Further studies are required to determine the clinical relevance (efficacy and safety) of this double absorption peak.
- *Food effect* A profound food effect on oral bioavailability was demonstrated, necessitating administration of desmopressin without concomitant food ingestion. The latter is rather difficult to achieve in younger children, though a dose regimen adaptation can be considered. However, the fed patients were older than 8 years of age and the young fasted patients only received a lyophilizate. Consequently, the food effect should be confirmed in fed young patients and fasted young patients receiving a tablet as well.
- *Bioequivalence and therapeutic equivalence* The claimed equivalence in adults (120-µg lyophilizate and 200-µg tablet) cannot just be extrapolated to children based on data obtained from clinical trials in adults alone. Observed differences in absorption of both formulations is probably attributed to a food and maturation effect. However, to be able to compare these formulations thoroughly, acquiring additional data (cfr. section double absorption peak and food effect) is required.
- *Dosing regimen* At the moment, flat dose regimens for the lyophilizate (60–480 µg) are applied for all children. However, these dosing regimens might not be appropriate since the target attainment is only 33.4%, resulting in suboptimal or too prolonged effects. It might be more appropriate to use bodyweight (< 4 years) or age-dependent (> 4 years) dose regimens as proposed by Michelet et al. [17]. These proposed dose regimens should be tested in a follow-up clinical trial, whereby the PD response measured by biomarkers (i.e. baseline urine osmolality, diuresis or aquaporin levels) should be considered. The same exercise should be performed for the tablet formulation. Moreover, in these trials, dose stratification by gender should be considered.
- *Study endpoints* In future studies it might be helpful to evaluate both anti-diuretic and anti-enuretic effect by performing a 1-day intensive PK/PD sampling, followed by the registration of the number of wet nights and diuresis in the following 14 days. The change or reduction of number of wet nights and the PK/PD of both formula-

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tions might be linked using, for example, time-to-event modeling.

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Compliance with Ethical Standards

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Conflict of Interest Elke Gasthuys, Lien Dossche, Robin Michelet, Jens Peter Nørgaard, Mathias Devreese, Siska Croubels, An Vermeulen, Jan Van Bocxlaer and Johan Vande Walle declare that they have no conflict of interest related to the manuscript.

Availability of Data and Material Data sharing not applicable to this article since no datasets were generated or analyzed during the current study.

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